REMARKS

Claims 1-15 are pending in the application.

Claim 16 was previously canceled. Claims 10 and 12 are canceled in this amendment.

Claims 1-7 are withdrawn from consideration.

Claim 8 has been amended to indicate that the method is directed to a patient in need of regeneration therapy and comprises administering mesenchymal stem cells and a mesenchymal stem cell migration-enhancing factor which enhances the migration and accumulation of the administered cells in an injured tissue or suppresses the diffusion of the administered cells from an injured tissue, to enhance regeneration of the injured tissue. Support for the amendment can be found in now canceled claim 10, as well as the Specification in Example 4, paragraph [0058], beginning on page 25 and paragraph [0060], which begins on page 27. The claim has also been amended by setting forth the full names of the various factors which had previously been listed in abbreviated form. Support for this amendment can be found in the Specification on page 2, line 26 (PDGF), page 3, line 5 (FGF), page 3, lines 12-13 (EGF), page 3, lines 18-19 (HB-EGF), page 7, lines 3-4 (IGF), page 7, line 4 (HGF) and page 22, line 12 (TGF-α) as well as the Diaclone Research Product Analysis sheet for Human TGF-α (attached).

New claims 17 and 18 have been added. Support for these claims can be found in the Specification in Example 4, paragraph [0058], beginning on page 25 and in paragraphs [0019], [0020], [0037] and [0039], as well as claims 13-15.

No new matter has been added.

Rejections Under 35 USC § 112, Second Paragraph

The Examiner has rejected claim 12 as indefinite for the use of the following abbreviations: EGF, HB-EGF, TGF-α, PDGF, FGF, IGF and HGF. The Examiner contends that these abbreviations can stand for various meanings.

Applicants have canceled claim 12, thereby obviating the rejection. Applicants note that the factors listed in claim 12 now appear in claim 8 and that the full names of the abbreviated factors are now listed.

The Examiner has rejected claims 8-15 as incomplete for omitting essential steps which amounts to a gap between the steps.

Applicants have amended the claims to state that the factor is administered to a patient in need thereof and that the regeneration of the injured tissue is enhanced, thereby overcoming the rejection.

Rejections Under 35 USC § 112, First Paragraph

Written Description

The Examiner has rejected claims 8-11 and 13-15 as failing to comply with the written description requirement. The Examiner contends that the claims read on any nucleic acid molecule, protein, peptide, antibody, small organic compound, cell or tissue that can enhance the migration and accumulation of mesenchymal stem cells in an injured tissue.

Applicants have incorporated the subject matter of claim 12 into claim 8. Claim 12 stated that the mesenchymal stem cell migration-enhancing factor is selected from the group consisting of Epidermal Growth Factor (EGF), Heparin Binding Epidermal Growth Factor (HB-EGF), Transforming Growth Factor-alpha (TGF-α), thrombin, Platelet-Derived Growth Factor (PDGF),

Fibroblast Growth Factor (FGF), hyaluronic acid, Insulin-like Growth Factor (IGF), and Hepatocyte Growth Factor (HGF). Applicants therefore request reconsideration and removal of the rejection.

Enablement

The Examiner has rejected claims 8-15 for lack of enablement. The Examiner contends that the Specification is not enabled for any nucleic acid molecule, protein, peptide, antibody, small organic compound, cell or tissue that can enhance the migration and accumulation of mesenchymal stem cells in an injured tissue. He also contends that the Specification fails to provide adequate guidance and evidence for how to use the claimed factors to provide regenerating injured tissue *in vivo* and states that the claims read on gene therapy *in vivo*. The Examiner also expresses concerns regarding administration of different proteins or peptides for regenerating injured tissue *in vivo*. Applicants respectfully traverse.

Applicants first note that claim 8 has been amended to recite that that the mesenchymal stem cell migration-enhancing factor is selected from the group consisting of Epidermal Growth Factor (EGF), Heparin Binding Epidermal Growth Factor (HB-EGF), Transforming Growth Factor-alpha (TGF-α), thrombin, Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF), hyaluronic acid, Insulin-like Growth Factor (IGF), and Hepatocyte Growth Factor (HGF).

Applicants next note that claim 8 now requires administering mesenchymal stem cells (MSCs) exogenously. Regarding routes of administration, MSCs can be administered by injection, for example by way of intravascular injection to the circulatory system or via intraperitoneal injections, as in Example 4, paragraph [0060] or as has been disclosed in the prior art (see paragraphs [0002] and [0003]). Similarly, the factor can be administered topically to the injured tissue by a separate route (see paragraph [0019]). For example, in Example 4 (see paragraph [0058]), PDGF-BB is administered by hypodermic injection in calves and mesenchymal stem cells (GFP-MSC) are injected into the tail vein. Furthermore, paragraphs

[0020], [0037] and [0039] disclose administering MSCs topically to the injured tissue or its periphery before, after or simultaneously with the administration of the factor.

Applicants submit that the disclosure of the Specification fulfills the enablement requirement and teaches how to make and use the claimed invention without undue experimentation. Therefore, Applicants respectfully request reconsideration and removal of the rejections.

Rejections Under 35 USC § 103

The Examiner has rejected claims 8-15 as obvious over each of Fiedler et al., Gerber et al., Badylak et al. or Desnoyers et al. The Examiner contends that Fiedler discloses that human platelet derived growth factor bb (rhPDGF-bb) can stimulate migration of primary human mesenchymal progenitor cells (MPC) in a dose-dependent manner. In the Examiner's opinion, this effect of rhPDGF-bb as a chemoattractive protein for primary human MPC suggests a functional role for recruitment of MPCs during bone development and remodeling. The Examiner states that MPCs are a type of mesenchymal stem cell.

With respect to Gerber, the Examiner states that this reference teaches that the growth factor HB-EGF stimulates mesenchymal cell proliferation and migration and promotes renal epithelial cell survival. The Examiner quotes "Answers.com, mesenchymal cell" to support his statement that a mesenchymal cell is also a mesenchymal stem cell.

According to the Examiner, Badylak teaches that growth factors FGF-2 and TGF-beta have been identified as particularly important to wound healing and tissue remodeling; FGF-2 promotes mesenchymal cell migration and proliferation to accelerate healing of gastric mucosa and calvarian bone. The Examiner again quotes "Answers.com, mesenchymal cell" to support his statement that a mesenchymal cell is also a mesenchymal stem cell.

Lastly, the Examiner contends that Desnoyers teaches that hyaluronic acid is a component of skin and mesenchymal tissue where it facilitates cell migration during wound healing. Once more the Examiner quotes "Answers.com, mesenchymal cell" to support his statement that a mesenchymal cell is also a mesenchymal stem cell.

The Examiner admits that Fiedler, Gerber, Badylak and Desnoyers do not specifically teach administration of rhPDGF-bb, HB-EGF FGF-2 or hyaluronic acid to injured tissue for regeneration therapy, administered simultaneously, continuously or separately, or administered topically, by injection or by applying over the injured tissue.

Nonetheless, the Examiner concludes that it would have been obvious for the skilled artisan to use rhPDGF-bb, HB-EGF FGF-2 or hyaluronic acid for regeneration therapy of injured tissue because Fiedler teaches that rhPDGF-bb can stimulate migration of primary human mesenchymal progenitor cells (MPC) in a dose-dependent manner, Gerber teaches HB-EGF stimulates mesenchymal cell proliferation and migration and promotes renal epithelial cell survival, Badylak teaches FGF-2 promotes mesenchymal cell migration and proliferation to accelerate healing of gastric mucosa and calvarian bone and that Desnoyers teaches that hyaluronic acid facilitates cell migration during wound healing. Applicants respectfully traverse.

Applicants first note that the claims have been amended to describe a method which comprises administering MSCs and a mesenchymal stem cell migration–enhancing factor to enhance regeneration of an injured tissue.

An object of the present invention is to provide therapeutic methods that may enhance the regeneration of injured tissue in osteoarthritis, bone fracture, loss of alveolar bone or jaw bone, cerebral infarction, myocardial infarction, lower limb ischemia, etc. by using substances that allow administered MSCs to accumulate specifically at injured sites or which prevent diffusion of administered MSCs (see paragraph [0007]).

The inventors found a chemotactic factor that enhances the migration and accumulation of administered MSCs and which also enhances the proliferation of MSCs. They learned that

agents and transplants that contained those chemotactic factors were effective in treatments for living tissue regeneration. The present invention has been accomplished on the basis of these findings (see paragraph [0008]).

The present invention is characterized in that the mesenchymal stem cell migration-enhancing factor is used as a chemotactic agent for guiding the injected MSCs; that is, it is used as a remote-controlling agent for the MSCs, which is capable of enhancing the migration and accumulation of the administered MSCs into an injured tissue and/or suppressing the diffusion of the administered mesenchymal stem cells from an injured tissue. This is supported by the *in vivo* results of Example 4, which shows that the GFP-MSCs migrated and accumulated in greater amounts at the site where PDGF-BB was localized (see paragraph [0060]).

As the Examiner acknowledges, none of the cited references teaches administration of a mesenchymal stem cell migration-enhancing factor to an injured tissue for regeneration therapy and none of the cited references remotely suggests administration of both MSCs and the factor. The cited references are totally silent about enhancing the migration and accumulation of the administered MSCs in an injured tissue or suppressing the diffusion of the administered MSCs from an injured tissue by the administration of both MSCs and the factor to enhance regeneration of the injured tissue.

In view of the above, Applicants respectfully request reconsideration and removal of the rejection.

Conclusion

In view of the above, all of the claims are submitted as defining non-obvious, patentable subject matter. Reconsideration of the rejections and allowance of the claims are respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Susan W. Gorman, Registration No. 47,604 at the telephone number of the undersigned below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: **January 22, 2010**

Respectfully submitted,

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Enclosure: Diaclone Research Product Analysis for Human TGF-α